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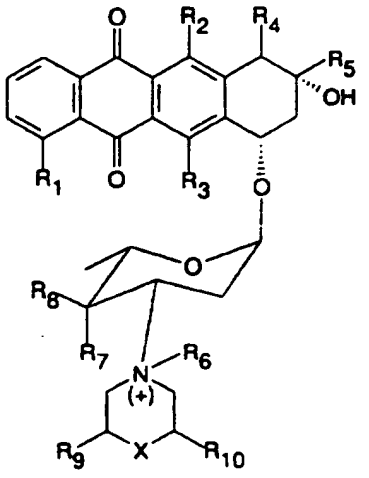
(54) Morpholine and piperidine N-oxide based anthracycline derivatives as antitumour agents

(57) Anthracycline analogue of formula A



A

[wherein R_1 is a hydrogen atom or a hydroxy or methoxy group; R_2 and R_3 are both hydroxy groups or one of R_2 and R_3 is a hydroxy group and the other of R_2 and R_3 is a hydrogen atom; R_4 is a hydrogen atom or a hydroxy, methoxy, carboxy or carbomethoxy group; R_5 is a group of formula $COCH_3$, $COCH_2OH$, CH_2CH_3, $CH(OH)CH_3$ or $CH(OH)CH_2OH$; R_6 is an oxygen atom or a hydroxy group; R_7 and R_8 are both hydrogen atoms or one of R_7 and R_8 is a hydroxy group, a halogen atom or the group OSO_2CH_3 and the other of R_7 and R_8 is a hydrogen atom; X is an oxygen atom or $-CH_2-$; R_9 and R_{10} are both hydrogen atoms or one of R_9 and R_{10} is a hydrogen atom and the other of R_9 and R_{10} is a hydroxy group or the group $O(CO)_nR_{11}$ in which R_{11} is a C_1-C_8 alkyl, C_3-C_8 cycloalkyl or phenyl C_1-C_6 alkyl group and n is 0 or 1, or one of R_9 and R_{10} is the group $O(CO)_nR_{11}$ as defined above and the other of R9 and R10 is a methyl or hydroxymethyl group; or a pharmaceutically acceptable salt thereof] are useful as antitumour agents, especially in the treatment of leukaemia or colon adenocarcinoma.

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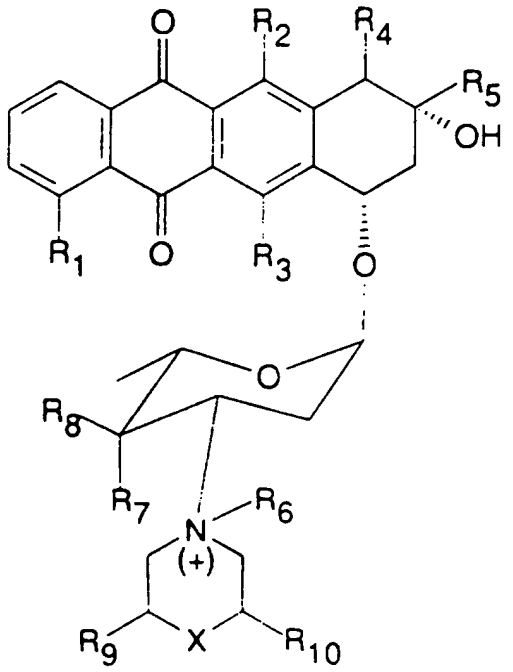
ANTHRACYCLINE DERIVATIVES

The present invention relates to new anthracycline analogues possessing antitumor activity, to a process for their preparation, and to pharmaceutical compositions containing them.

The present invention provides a compound which is an anthracycline analogue of formula A



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wherein R_1 is a hydrogen atom or a hydroxy or methoxy group; R_2 and R_3 are both hydroxy groups or one of R_2 and R_3 is a hydroxy group and the other of R_2 and R_3 is a hydrogen atom; R_4 is a hydrogen atom or a hydroxy, methoxy, carboxy or carbomethoxy group; R_5 is a group of formula $COCH_3$, $COCH_2OH$, CH_2CH_3, $CH(OH)CH_3$ or $CH(OH)CH_2OH$; R_6 is an oxygen atom or a hydroxy group; R_7 and R_8 are both hydrogen atoms or one of R_7 and R_8 is a

other of R_7 and R_8 is a hydrogen atom; X is an oxygen atom or $-CH_2-$; R_9 and R_{10} are both hydrogen atoms or one of R_9 and R_{10} is a hydrogen atom and the other of R_9 and R_{10} is a hydroxy group or the group $O(CO)_nR_{11}$ in which R_{11} is a C_1-C_8 alkyl, C_3-C_8 cycloalkyl or phenyl C_1-C_6 alkyl group and n is 0 or 1, or one of R_9 and R_{10} is the group $O(CO)_nR_{11}$ as defined above and the other of R_9 and R_{10} is a methyl or hydroxymethyl group; or a pharmaceutically acceptable salt thereof.

In this specification, the hydrocarbon chain of the alkyl, alkoxy and acyloxy groups may be a straight or a branched chain.

Preferably, C_1-C_8 alkyl is methyl, ethyl, n-propyl, iso-proyl, n-butyl, t-butyl, sec-butyl or n-pentyl.

Preferably, C_3-C_8 cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

Preferably, phenyl C_1-C_6 alkyl is benzyl, phenylpropyl or phenylbutyl.

Preferably ions of pharmaceutically acceptable salt derivatives according to the invention are those derived from pharmaceutically acceptable acids, both inorganic acids such as hydrochloric acid and organic acids such as acetic, methanesulfonic or ethanesulfonic acid.

The present invention encompasses all the possible stereoisomers as well as their racemic or optically active mixtures. In such case (S) and (R) mean the configuration of a substituted carbon atom.

A preferred class of compounds according to the invention are the compounds of formula A, wherein R_6 is oxygen or hydroxy, more preferably hydroxy, X is oxygen or CH_2, more preferably oxygen, and R_1 is hydrogen or methoxy, R_2 and R_3 are both hydroxy, R_4 is hydrogen, R_5 is a group of formula $COCH_3$, $COCH_2OH$ or $COCH(OH)CH_2OH$, R_9 and R_{10} are both hydrogen atoms or one of R_9 and R_{10} is hydrogen and the other of R_9 and R_{10} is methoxy, preferably in the optically active configuration (S) or (R), R_7 is hydroxy and R_8 is hydrogen.

Example of specific preferred compounds of the invention

(A1):3'-deamino-3'[2(S)-methoxy-4-morpholinyl]-doxorubicin N-oxide
[R_1=OCH_3, R_2=R_3=OH, R_4=H, R_5=$COCH_2OH$, R_6=O, R_9=H, R_{10}=(S)OCH_3, X=O, R_7=OH, R_8=H]

(A2):3'-deamino-3'[2(S)-methoxy-4-morpholinyl]-doxorubicin N-hydroxide chloride
[R_1=OCH_3, R_2=R_3=OH, R_4=H, R_5=$COCH_2OH$, R_6=OH, R_9=H, R_{10}=(S)OCH_3, X=O, R_7=OH, R_8=H]

(A3):3'-deamino-3'[2(R)-methoxy-4-morpholinyl]-doxorubicin N-oxide
[R_1=OCH_3, R_2=R_3=OH, R_4=H, R_5=$COCH_2OH$, R_6=O, R_9=H, R_{10}=(R)OCH_3, X=O, R_7=OH, R_8=H]

(A4): 3'-deamino-3'[2(R)-methoxy-4-morpholinyl]-doxorubicin N-hydroxide chloride
[R_1=OCH_3, R_2=R_3=OH, R_4=H, R_5=$COCH_2OH$, R_6=OH, R_9=H, R_{10}=(R)OCH_3, X=O, R_7=OH, R_8=H]

(A5):4-demethoxy-3'-deamino-3'[2(S)-methoxy-4-morpholinyl]-daunorubicin N-oxide
[R_1=H, R_2=R_3=OH, R_4=H, R_5=$COCH_3$, R_6=O, R_9=H, R_{10}=(S)OCH_3, X=O, R_7=OH, R_8=H]

(A6):4-demethoxy-3'-deamino-3'[2(S)-methoxy-4-morpholinyl]-daunorubicin N-hydroxide chloride
[R_1=H, R_2=R_3=OH, R_4=H, R_5=$COCH_3$, R_6=OH, R_9=H, R_{10}=(S)OCH_3, X=O, R_7=OH, R_8=H]

(A7):4-demethoxy-3'-deamino-3'[2(R)-methoxy-4-morpholinyl]-daunorubicin N-oxide
[R_1=H, R_2=R_3=OH, R_4=H, R_5=$COCH_3$, R_6=O, R_9=H, R_{10}=(R)OCH_3, X=O, R_7=OH, R_8=H]

(A8):4-demethoxy-3'-deamino-3'[2(R)-methoxy-4-morpholinyl]-daunorubicin N-hydroxide chloride
[R_1=H, R_2=R_3=OH, R_4=H, R_5=$COCH_3$, R_6=OH, R_9=H, R_{10}=(R)OCH_3, X=O, R_7=OH, R_8=H]

(A9):3'-deamino-3'[4-morpholinyl]-doxorubicin N-oxide
[R_1=OCH_3, R_2=R_3=OH, R_4=H, R_5=$COCH_2OH$, R_6=O, R_9=R_{10}=H, X=O, R_7=OH, R_8=H]

(A10):3'-deamino-3'[4-morpholinyl]-doxorubicin N-hydroxide

$X=O$, $R_7=OH$, $R_8=H$]

(A11):13-dihydro-3'-deamino-3'[2-methoxy-4-morpholinyl]-doxorubicin N-oxide

[$R_1=OCH_3$, $R_2=R_3=OH$, $R_4=H$, $R_5=CH(OH)CH_2OH$, $R_6=O$, $R_9=H$, $R_{10}=OCH_3$, $X=O$, $R_7=OH$, $R_8=H$]

(A12):13-dihydro-3'-deamino-3'[2-methoxy-4-morpholinyl]-doxorubicin N-hydroxy chloride

[$R_1=OCH_3$, $R_2=R_3=OH$, $R_4=H$, $R_5=CH(OH)CH_2OH$, $R_6=OH$, $R_9=H$, $R_{10}=OCH_3$, $X=O$, $R_7=OH$, $R_8=H$]

(A13):3'-deamino-3'[piperidine]-doxorubicin N-oxide

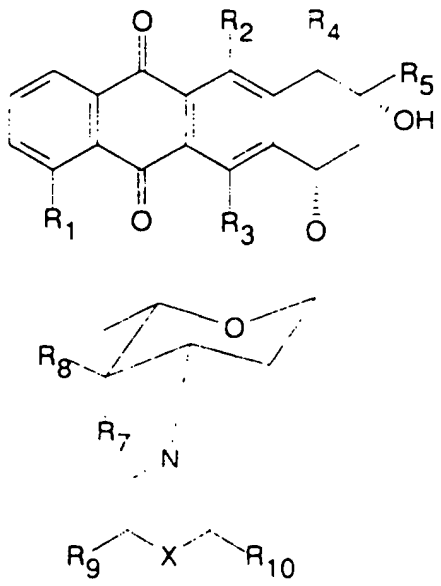
[$R_1=OCH_3$, $R_2=R_4=OH$, $R_4=H$, $R_5=COCH_2OH$, $R_6=O$, $R_9=R_{10}=H$, $X=CH_2$, $R_7=OH$, $R_8=H$]

(A14):3'-deamino-3'[piperidine]-doxorubicin N-hydroxy chloride

[$R_1=OCH_3$, $R_2=R_3=OH$, $R_4=H$, $R_5=COCH_2OH$, $R_6=OH$, $R_9=R_{10}=H$, $X=CH_2$, $R_7=OH$, $R_8=H$]

Anthracyclines N-oxide of formula A ($R_6=O$) may be prepared by a process which comprises:

i) reacting a compound of formula B



R_1, R_2, R_3, R_4, R_5, R_7, R_8, R_9, R_{10} and X are as defined

above with a peroxide compound.

Anthracyclines N-hydroxide of formula A (R_6=OH) may be prepared by (ii) reacting the resultant N-oxide derivative of formula A with an organic or inorganic acid.

For example, a preferred process for the preparation of anthracycline N-oxides of formula A comprises treating a compound of formula B as previously defined, in the form of a free base, in organic apolar solvent such as acetone, with a peroxide compound such as dimethyldioxirane at temperature from -40°C to -10°C, preferably at -30°C, for from 5 to 30 minutes, then removing the solvent under reduced pressure and purifing the resultant N-oxide derivative, for example by flash chromatography on silica gel.

A preferred process for the preparation of anthracycline N-hydroxide of formula A comprises treating the anthracycline N-oxide, dissolved in an organic solvent such as methylene chloride, with an anhydrous acid, preferably anhydrous hydrogen chloride, at a temperature of from -10°C to 0°C, preferably -5°C.

Dimethyldioxirane may be prepared as described in J.Org.Chem., 1987, vol 52, 2800-2803.
It should be noted that the use of dimethyldioxirane allows the formation of anthracycline N-oxide without formation of by-products. In addition, this reagent is easily removed from the reaction mixture under reduced pressure.

The starting anthracyclines, namely morpholino or morpholino ring substituted or piperidine derivatives, of formula B are well known from the literature, see Bioactive Molecules Vol.6, edited by J.W.Lown (Elsevier 1988). Preferred starting compounds are:

(B1) 3'-deamino-3'[2(S)-methoxy-4-morpholinyl]-doxorubicin [R_1=OCH_3, R_2=R_3=OH, R_4=H, R_5=$COCH_2OH$, R_9=H, R_{10}=(S)OCH_3, X=O, R_7=OH, R_8=H],

(B2) 3'-deamino-3'[2(R)-methoxy-4-morpholinyl]-doxorubicin [R_1=OCH_3, R_2=R_3=OH, R_4=H, R_5=$COCH_2OH$, R_9=H, R_{10}=(R)OCH_3, X=O, R_7=OH, R_8=H]

(B3) 4-demethoxy-3'-deamino-3'[2(S)-methoxy-4-morpholinyl]

[R_1=H, R_2=R_3=OH, R_4=H, R_5=$COCH_3$, R_9=H, R_{10}=(S)OCH_3, X=O, R_7=OH, R_8=H]

(B4) 4-demethoxy-3'-deamino-3'[2(R)-methoxy-4-morpholinyl] daunorubicin
[R_1=H, R_2=R_3=OH, R_4=H, R_5=$COCH_3$, R_9=H, R_{10}=(R)OCH_3, X=O, R_7=OH, R_8=H]

(B5) 3'-deamino-3'[4-morpholinyl]-doxorubicin
[R_1=OCH_3, R_2=R_3=OH, R_4=H, R_5=$COCH_2OH$, R_9=R_{10}=H, X=O, R_7=OH, R_8=H]

(B6) 13-dihydro-3'-deamino-3'[2-methoxy-4-morpholinyl]-doxorubicin

(B7) 3'-deamino-3'[piperidine]-doxorubicin
[R_1=OCH_3, R_2=R_3=OH, R_4=H, R_5=$COCH_2OH$, R_9=R_{10}=H, X=CH_2, R_7=OH, R_8=H]

The new anthracycline derivatives of the present invention are water soluble, also in the form of an N-oxide. Surprisingly, while the N-oxide derivatives of formula A (R_6=O) show cytotoxic activity on tumor cells similar to those of the starting anthracyclines of formula B, the corresponding N-hydroxide derivatives A (R_6=OH) are from 10 to 100 fold more potent than the corresponding N-oxide.

The present invention also provides a pharmaceutical composition comprising a pharmaceutically acceptable diluent or carrier and, as an active principle, as anthracycline analogue of formula A or a pharmaceutically acceptable salt thereof.

Suitable routes of administration include parenteral administration. For parenteral administration a liquid formulation may be prepared using the active compound and a sterile diluent or carrier which may either dissolve the active compound or provide a suspension for it. The parenteral formulation may be prepared in the form of a sterile solid for reconstitution prior to administration with a suitable vehicle such as physiological saline, sterile water or other sterile vehicle.

The compounds of the invention are useful in methods of treatment of the humam and animal body by therapy. They are [illegible] tumor agents in particular in the treatment of

leukaemia or colon adenocarcinoma. A therapeutically effective amount is administered to a patient having a tumor to ameliorate or improve the condition of the patient. An amount sufficient to inhibit the growth of the tumor may be administered. The dosage to be given can be ascertained using known dosage ranges for doxorubicin and daunorubicin modified by reference to the activity shown by the present compounds in in vitro and in vivo anti-tumor tests. Suitable dosages are generally in the range of 1 to 200 mg/m^2 body surface, preferably from 1 to 100 mg/m^2, depending on the nature and severity of the disease being treated and on the general condition of the patient.

The following Examples further illustrate the present invention.

Example 1
3'-deamino-3'[2(S)-methoxy-4-morpholinyl]-doxorubicin N-oxide (A1)

3'-deamino-3'[2(S)-methoxy-4-morpholinyl]-doxorubicin (B1: 0.44g
0.6 mmole) is dissolved in anhydrous acetone (20 ml) at -30°C and treated with a 0.1M solution of dimethyldioxirane in acetone (10 ml) for 30 minutes. Then the reaction mixture is concentrated under reduced pressure and the crude material is flash chromatographed on silica gel using a mixture of methylene chloride and methanol (90:10 by volume) as an eluting system to give the title compound A1 (0.36 g).
TLC on Kieselgel plate F254 (Merck), eluting system methylene chloride, methanol, acetic acid, water (30:4:1:0.5 by volume) Rf:0.6.

Example 2
3'-deamino-3'[2(S)-methoxy-4-morpholinyl]-doxorubicin N-hydroxide chloride (A2)

Compound A1 (0.18g, 0.22 mmole), prepared as described in Example 1, is dissolved in anhydrous methylene chloride (5 ml)

at 0°C and added with an equivalent amount of 0.1M methanolic solution of anhydrous hydrogen chloride. The title compound (A2, 0.22 g) is precipitated by adding a mixture of ethyl ether and petroleum ether (100 ml).
TLC on Kieselgel plate F254 (Merck), eluting system methylene chloride, methanol, acetic acid, water (30:4:1:0.5 by volume) Rf:0.6.

Example 3
3'-deamino-3'[2(R)-methoxy-4-morpholinyl]-doxorubicin N-oxide (A3)

Compound A3 is prepared from 3'-deamino-3'[2(R)-methoxy-4-morpholinyl]-doxorubicin (B2) following the same procedure described in Example 1.
TLC on Kieselgel plate F254 (Merck), eluting system methylene chloride, methanol, acetic acid, water (30:4:1:0.5 by volume) Rf:0.63

Example 4
3'-deamino-3'[2(R)-methoxy-4-morpholinyl]-doxorubicin N-hydroxide chloride (A4)

Compound A4 is prepared from compound A3, prepared as described in Example 3, following the same procedure described in Example 2. TLC on Kieselgel plate F254 (Merck), eluting system methylene chloride, methanol, acetic acid, water (30:4:1:0.5 by volume) Rf:0.63

Example 5
4-demethoxy-3'-deamino-3'[2(S)-methoxy-4-morpholinyl] daunorubicin N-oxide (A5)

Compound A5 is prepared from 4-demethoxy-3'-deamino-3'[2(S)-methoxy-4-morpholinyl] (B3) following the same procedure described in Example 1. TLC on Kieselgel plate F254 (Merck), eluting system methylene chloride, methanol (20:1 by volume) Rf:0.28

Example 6
4-demethoxy-3'-deamino-3'[2(S)-methoxy-4-morpholinyl] daunorubicin N-hydroxide chloride (A6)

Compound A6 is prepared from compound A5, prepared as described in Example 5, following the same procedure described in Example 2. TLC on Kieselgel plate F254 (Merck), eluting system methylene chloride, methanol (20:1 by volume) Rf:0.28

Example 7
3'-deamino-3'[4-morpholinyl]-doxorubicin N-oxide (A9)

Compound A9 is prepared from 3'-deamino-3'[4-morpholinyl]-doxorubicin (B5) following the same procedure described in Example 1. TLC on Kieselgel plate F254 (Merck), eluting system methylene chloride, methanol, acetic acid, water (30:4:1:0.5 by volume) Rf:0.37

Example 8
3'-deamino-3'[4-morpholinyl]-doxorubicin N-hydroxide (A10)

Compound A10 is prepared from compound A9, prepared as described in Example 7, following the same procedure described in Example 2. TLC on Kieselgel plate F254 (Merck), eluting system methylene chloride, methanol, acetic acid, water (30:4:1:0.5 by volume) Rf:0.37

Biological Activity

3'-deamino-3'[2(S)-methoxy-4-morpholinyl] doxorubicin N-oxide (A1) and 3'-deamino-3'[2(S)-methoxy-4-morpholinyl] doxorubicin N-hydroxide (A2) were tested *in vitro* on L1210, 48 h treatment, in comparison with 3'-deamino-3'[2(S)-methoxy-4-morpholinyl] doxorubicin (B1). The cytotoxic activity is reported as IC50, the concentration inhibiting 50% of colony formation, calculated on concentration response curves. The N-hydroxy

derivative of formula (A2) was found to be 20 fold more potent than the parent compound B1 (Table 1)

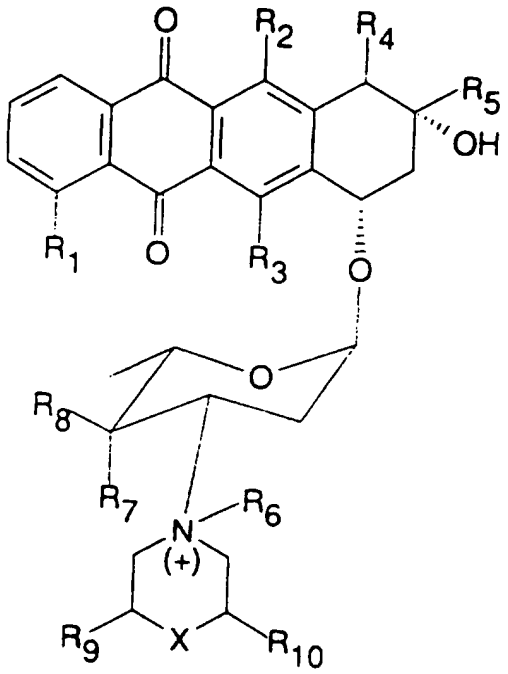
Table 1: in vitro cytotoxic activity (IC50) of 3'-deamino-3'[2(S)-methoxy-4-morpholinyl] doxorubicin N-oxide (A1) and 3'-deamino-3'[2(S)-methoxy-4-morpholinyl] doxorubicin N-hydroxide (A2) on L1210 cells in comparison with 3'-deamino-3'[2(S)-methoxy-4-morpholinyl]doxorubicin (B1).

Compound	IC50 (ng/ml)
A1	5.43
A2	0.36
B1	7.62

Colony assay: 48h treatment.

CLAIMS

1. A compound which is an anthracycline analogue of formula A



A

wherein R_1 is a hydrogen atom or a hydroxy or methoxy group; R_2 and R_3 are both hydroxy groups or one of R_2 and R_3 is a hydroxy group and the other of R_2 and R_3 is a hydrogen atom; R_4 is a hydrogen atom or a hydroxy, methoxy, carboxy or carbomethoxy group; R_5 is a group of formula $COCH_3$, $COCH_2OH$, CH_2CH_3, $CH(OH)CH_3$ or $CH(OH)CH_2OH$; R_6 is an oxygen atom or a hydroxy group; R_7 and R_8 are both hydrogen atoms or one of R_7 and R_8 is a hydroxy group, a halogen atom or the group OSO_2CH_3 and the other of R_7 and R_8 is a hydrogen atom; X is an oxygen atom or $-CH_2-$; R_9 and R_{10} are both hydrogen atoms or one of R_9 and R_{10} is a hydrogen atom and the other of R_9 and R_{10} is a hydroxy group or the group $O(CO)_nR_{11}$ in which R_{11} is a C_1-C_8 alkyl, C_3-C_8 cycloalkyl or phenyl C_1-C_6 alkyl group and n is 0 or 1, or one of R_9 and R_{10} is the group $O(CO)_nR_{11}$ as defined above and the other of R_9 and R_{10} is a methyl or hydroxymethyl group; or a

2. A compound according to claim 1 wherein R_6 is a hydroxy group.

3. A compound according to claim 1 or 2 wherein X is an oxygen atom.

4. A compound according to any one of claims 1 to 3 wherein R_1 is hydrogen or methoxy, R_2 and R_3 are both hydroxy, R_4 is hydrogen, R_5 is a group of formula $COCH_3$, $COCH_2OH$ or $COCH(OH)CH_2OH$ and R_9 and R_{10} are both hydrogen atoms.

5. A compound according to any one of claims 1 to 4 wherein R_7 is a hydroxy group and R_8 is a hydrogen atom;

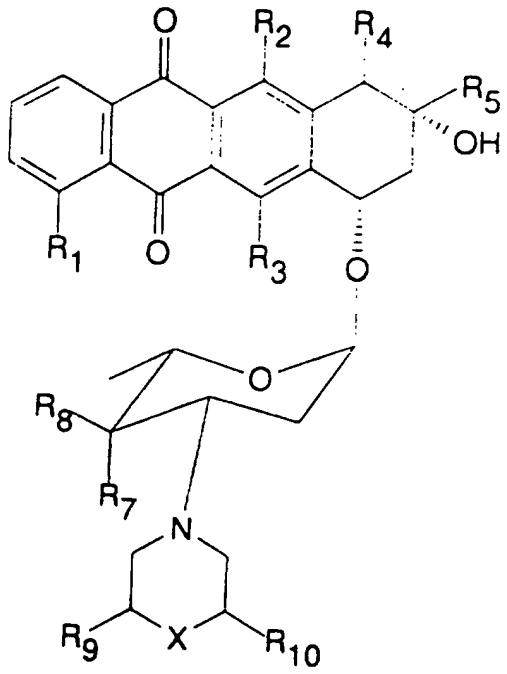
6. A compound according to claim 1 which is
3'-deamino-3'[2(S)-methoxy-4-morpholinyl]-doxorubicin N-oxide,
3'-deamino-3'[2(S)-methoxy-4-morpholinyl]-doxorubicin N-hydroxide chloride,
3'-deamino-3'[2(R)-methoxy-4-morpholinyl]-doxorubicin N-oxide,
3'-deamino-3'[2(R)-methoxy-4-morpholinyl]-doxorubicin N-hydroxide chloride,
4-demethoxy-3'-deamino-3'[2(S)-methoxy-4-morpholinyl]-daunorubicin N-oxide,
4-demethoxy-3'-deamino-3'[2(S)-methoxy-4-morpholinyl]-daunorubicin N-hydroxide chloride,
4-demethoxy-3'-deamino-3'[2(R)-methoxy-4-morpholinyl]-daunorubicin N-oxide,
4-demethoxy-3'-deamino-3'[2(R)-methoxy-4-morpholinyl]-daunorubicin N-hydroxide chloride,
3'-deamino-3'[4-morpholinyl]-doxorubicin N-oxide,
3'-deamino-3'[4-morpholinyl]-doxorubicin N-hydroxide,
13-dihydro-3'-deamino-3'[2-methoxy-4-morpholinyl]-doxorubicin N-oxide,
13-dihydro-3'-deamino-3'[2-methoxy-4-morpholinyl]-doxorubicin N-hydroxy chloride,
3'-deamino-3'[piperidine]-doxorubicin N-oxide or
3'-deamino-3'[piperidine]-doxorubicin N-hydroxychloride.

7. A compound according to any one of the preceding claims which is in the form of its hydrochloride salt.

8. A process for the preparation of a compound which is

an anthracycline analogue of formula A or a pharmaceutically acceptable salt thereof as defined in any one of the preceding claims, which process comprises

(a) reacting with a peroxide compound a compound of formula B



B

wherein R_1, R_2, R_3, R_4, R_5, R_7, R_8, R_9, R_{10} and X are as defined in claim 1, and, if desired

(b) treating the resultant N-oxide with an organic or inorganic acid and, if desired,

(c) converting the anthracycline analogue of formula A thus obtained into a pharmaceutically acceptable salt thereof.

9. A process according to claim 8 wherein step (a) is carried out in an organic apolar solvent and the peroxide compound is dimethyldioxirane.

10. A process according to claim 9 wherein the organic apolar solvent is acetone.

11. A process according to any one of claims 8 to 10

wherein step (a) is conducted at a temperature of from -40° to -10°C for from 5 to 30 minutes.

12. A process according to any one of claims 8 to 11 wherein step (b) is carried out in an organic solvent and the acid is anhydrous hydrogen chloride.

13. A process according to claim 12 wherein the organic solvent is methylene chloride.

14. A process according to claim 12 or 13 which is carried out at a temperature of from -10°C to 0°C.

15. A compound according to claim 1 specifically identified herein.

16. A process for preparing a compound as defined in claim 1 which process is substantially as described in any one of Examples 1 to 8.

17. A pharmaceutical composition comprising a pharmaceutically acceptable diluent or carrier and, as an active principle, an anthracycline analogue of formula A or a pharmaceutically acceptable salt thereof, as defined in any one of claims 1 to 7 or 15.

18. An anthracycline analogue of formula A or a pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 7 or 15 for use in a method of treatment of the human or animal body by therapy.

19. An anthracycline analogue of formula A or a pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 7 or 15 for use as an anti-tumor agent.

20. Use of an anthracycline analogue of formula A or a pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 7 or 15 in the manufacture of a medicament for the treatment of a tumor.

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Databases (see below) (i) UK Patent Office collections of GB, EP, WO and US patent specifications. (ii) ONLINE: CAS ONLINE	Documents considered relevant following a search in respect of Claims :- 1-20

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